Response to the Office Action

Applicants respectfully submit that the Examiner has not met the burden of establishing a reasonable basis to question the enablement provided for the claimed invention.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. *U.S. v. Teletronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); *In re Stephens*, 188 USPQ 659, 661 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987).

Information Known in the Art: First generation adenoviral vectors had been constructed and used for the transfer of genes, both *in vitro* and *in vivo*, before the filing dates of Applicants' French priority applications (13 July 1993 and 18 April 1994). The following publications are illustrative of the state of the art at the time of Applicants' priority applications.

In 1985, Ballay et al. described how defective adenovirus vectors could be used to transfer and express foreign genes both *in vitro* and *in vivo* (EMBO Journal 4(13B): 3861-65, 1985, attached as EXHIBIT A). The authors constructed recombinant defective adenoviruses containing the pre-S2 region and the S gene of hepatitis B virus. When transferred into cultured cells, the recombinant adenoviruses expressed authentic hepatitis B surface antigen particles carrying a pHSA receptor activity. When injected into animals the recombinant adenoviruses elicited the production of anti-HBs and anti-pHSA receptor antibodies. The authors commented that recombinant adenoviruses such as those described could be used both to protect against hepatitis B viral infections and to treat hepatitis B viral infections.

In 1991, Levrero et al. described how defective adenovirus vectors could be used to transfer and express foreign genes both *in vitro* and *in vivo* (Gene 101: 195-202, attached as EXHIBIT B). The authors constructed recombinant defective adenoviruses containing a gene encoding either the hepatitis B surface antigen or bacterial chloramphenicol acetyltransferase. When transferred into cultured cells, the recombinant adenoviruses expressed the

foreign genes at high levels, and the authors concluded that "adenovirus can be a generally useful vector to express foreign genes at high levels in a wide spectrum of cells." Id. at 200. When injected into chimpanzees the recombinant adenoviruses were able to immunologically prime the animals, resulting in a partial protection against hepatitis B virus challenge.

In 1993, Bajocchi et al. described how defective adenovirus vectors could be used to transfer and express foreign genes *in vivo* (Nature Genetics 3:229-34, 1993, previously cited by the Examiner and attached as EXHIBIT C). The authors constructed recombinant defective adenoviruses containing a gene encoding either ß-galactosidase or human α1-antitrypsin. Upon transfer of the recombinant viruses to the lateral ventricle of rats, ß-galactosidase was transferred to the ependymal cells lining the ventricles or α1-antitrypsin was secreted into the cerebral spinal fluid. Following the stereotactic administration of the ß-galactosidase vectors into the globus pallidus, ß-galactosidase activity was detected in the globus pallidus and the substantia nigra.

These publications, as well as numerous others that could be cited, show that before Applicants' priority filing dates, adenoviral vectors had been described and used for the transfer and expression of genes both *in vitro* and *in vivo*. The prior art vectors, however, had various disadvantages including the production of replication competent virus, the expression of numerous viral genes, and a limited capacity for foreign DNA.

Applicants' Claimed Invention: Applicants' claimed invention overcomes these disadvantages of prior art vectors by providing recombinant adenoviruses which are replication defective, which have multiple deletions in the adenoviral genome, and which have the capacity to accept large heterologous DNA sequences.

Applicants' claims are directed to third generation defective recombinant adenoviral vectors and to cell lines used to prepare third generation defective recombinant adenoviral vectors. The claims do not recite any particular environment of use. As disclosed in the specification, Applicants' claimed invention can be used in *in vivo* gene therapy. Among the other well known uses of Applicants' claimed invention are use in *ex vivo* gene therapy, use in the *in vitro* production of proteins, use as a research tool, and use in vaccines to elicit a protective or curative immune response (as discussed in the specification at page 6, line 29 to page 8, line 15).

Applicants' Disclosure: Applicants' specification discloses the detailed construction of adenoviral vectors which are replication defective, which have multiple deletions in the adenoviral genome, and which have the

capacity to accept large heterologous DNA sequences. The specification discloses that these vectors can be used to transfer genes into cells, and for the treatment or prevention of numerous pathologies:

> "The present invention indeed describes recombinant adenoviruses for gene therapy, which are capable of efficiently transferring DNA (up to 30 kb) in vivo, of expressing at high levels and in a stable manner this DNA in vivo, while limiting any risk of production of viral proteins, of transmission of the virus, of pathogenicity and the like."
>
> Specification at page 2, lines 29-35.

The Examiner's Rejection: The Examiner asserted that the specification provides insufficient guidance on how to use the claimed vectors. To support this rejection the Examiner cited quotations from several references as evidence that *in vivo* human gene therapy is not yet a predictable art, then concluded that it would require undue experimentation for those skilled in the art to practice the invention.

Applicants respectfully submit that this rejection does not meet the PTO's initial burden of establishing lack of enablement because: (1) the Examiner has not established a reasonable basis to question the enablement of Applicants' claimed invention for *in vivo* gene therapy, and (2) the Examiner has provided no basis for questioning the enablement of any of the other well known uses of Applicants' claimed invention.

With respect to the enablement of Applicants' claimed invention for *in vivo* gene therapy, the Examiner has failed to adequately explain the reasons for doubting the objective truth of Applicants' statements that the claimed vectors and cells can be used to transfer therapeutic genes *in vivo*. The Examiner states that the specification does not disclose the proper modes of administration of the claimed adenoviral vectors. Applicants point out that the specification discloses methods of administration at page 12, lines 14-34. Applicants further point out that one of ordinary skill in the art knows how, without undue experimentation, to administer adenoviruses to cells (*in vitro* AND *in vivo*). The Examiner next states that even though the specification discloses the doses of recombinant adenoviruses to be used (at page 12, line 35 to page 13, line 6), the specification does not provide enabling support for

these concentrations. Applicants point out that one of ordinary skill in the art is familiar with, or can determine without undue experimentation, the doses of recombinant adenoviruses to be used for the transfer of genes into cells (*in vitro* AND *in vivo*). Finally, the Examiner presents several quotations, all outside of their original context, as supporting the assertion that *in vivo* gene therapy is an unpredictable art. Applicants respectfully submit that these general statements do not meet the PTO's burden of explaining why undue experimentation would be needed to enable one of ordinary skill in the art to transfer genes to cells using Applicants' claimed invention. Furthermore, Applicants are prepared to present other quotations, also by those of skill in the art, extolling the enormous promises and modest successes of gene therapy.

Moreover, Applicants respectfully submit that the Examiner's emphasis on the unpredictability of gene therapy is somewhat misplaced, because the claims are not limited to gene therapy and because there are several other well known uses for Applicants' claimed invention. The Examiner has provided no basis for questioning the enablement of Applicants' claimed invention for use in *ex vivo* gene therapy, for use in the *in vitro* production of proteins, for use as a research tool, or for use in vaccines to elicit a protective or curative immune response. Applicants submit that the level of skill in the art of gene transfer is high, and that the ordinary skilled artisan, given the benefit of Applicants' disclosure, could use the claimed invention for any of these purposes without undue experimentation.

Conclusion: One of skill in the art, having the benefit of Applicants' disclosure coupled with information known in the art, could make and use applicants' claimed invention for a variety of purposes without undue experimentation. Applicants respectfully submit that the Examiner has not met the PTO's initial burden of establishing lack of enablement because the Examiner has not established a reasonable basis to question the enablement of Applicants' claimed invention for *in vivo* gene therapy, and because the Examiner has not provided a basis for questioning the enablement of any of the other well known uses of Applicants' claimed invention. In view of this, Applicants request reconsideration and withdrawal of the rejection of claims 1-3, 6, and 9-35 under 35 U.S.C. § 112, first paragraph.

Once the § 112, 2d paragraph rejection has been withdrawn, this application should be in condition for allowance. Applicants therefore respectfully request favorable reconsideration and an action passing this case to issue.

In the event that a telephone interview would be helpful in advancing the prosecution of this application, Applicants' agent invites the Examiner to contact Mr. Savitzky at the number shown below.

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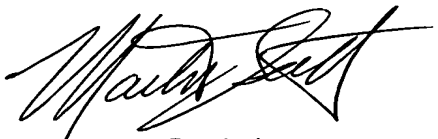

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APPENDIX
U.S. Patent Application Serial No. 08/397,225
"DEFECTIVE ADENOVIRUS VECTORS AND
USE THEREOF IN GENE THERAPY"
RPR File No. EX93015G1-US
Claims Under Consideration

1. (Twice Amended) A defective recombinant adenovirus comprising
the ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein the E1 gene has been rendered non-functional by deletion, and wherein the E2 or E4 genes have been rendered non-functional by deletion.

2. (Amended) An adenovirus according to claim 1, characterized in that the adenovirus sequences are from a canine adenovirus.

3. (Twice Amended) An adenovirus according to claim 1, characterized in that the adenovirus sequences are from a human group C adenovirus.

6. (Twice Amended) An adenovirus according to claim 1, characterized in that the late genes L1-L5 have been rendered non-functional by deletion.

9. (Amended) An adenovirus according to claim 1, characterized in that the E3 gene has been rendered non-functional by deletion.

10. (Amended) An adenovirus according to claim 9, characterized in that the L5 gene has been rendered non-functional by deletion.

11. (Twice Amended) An adenovirus according to claim 1, further comprising a functional E3 gene under the control of a heterologous promoter.

12. (Twice Amended) An adenovirus according to claim 1, characterized in that the heterologous DNA sequence is selected from the group consisting of therapeutic genes and genes encoding antigenic peptides.

13. (Twice Amended) An adenovirus according to claim 12, characterized in that the heterologous DNA is a therapeutic gene which encodes a product selected from the group consisting of enzymes, blood derivatives, hormones, lymphokines, growth factors, neurotransmitters, precursors of neurotransmitters, synthetic enzymes, trophic factors, apolipoproteins, dystrophin, minidystrophin, tumor suppressor genes, and genes encoding factors involved in coagulation.

14. (Amended) An adenovirus according to claim 1, characterized in that the heterologous DNA encodes an antisense sequence.

15. (Amended) An adenovirus according to claim 12, characterized in that the heterologous DNA encodes an antigenic peptide capable of generating an immune response against microorganisms, tumors, or viruses.

16. (Amended) An adenovirus according to claim 15, characterized in that the gene encodes an antigenic peptide specific for a virus selected from the group consisting of the Epstein Barr virus, the HIV virus, the hepatitis B virus, and the pseudo-rabies virus.

17. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a promoter.

18. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence.

19. (Twice Amended) A cell line comprising, integrated into its genome, the genes necessary to complement a defective recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Twice Amended) A cell line according to claim 19, characterized in that it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Amended) A cell line according to claim 20, characterized in that it additionally comprises the E4 gene from an adenovirus.

22. (Twice Amended) A cell line according to claim 19, characterized in that it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Twice Amended) A cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Twice Amended) A cell line according to claim 19, characterized in that it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Amended) A cell line according to claim 19, characterized in that the inducible promoter is the LTR promoter of MMTV.

26. (Twice Amended) A cell line according to claim 19, characterized in that it comprises a gene encoding the 72 K protein of E2.

27. (Amended) A cell line according to claim 19, characterized in that it is obtained from the line 293.

28. (Twice Amended) A composition comprising a defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Twice Amended) A composition comprising a recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Twice Amended) A composition according to claim 28 wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

31. (Amended) A defective recombinant adenovirus comprising

the ITR sequences,

an encapsulation sequence, and

a heterologous DNA sequence,

wherein the E3 and E4 genes have been rendered non-functional by deletion.

32. An adenovirus according to claim 31, characterized in that the late genes L1-L5 have been rendered non-functional by deletion.

33. A cell line according to claim 19, characterized in that it comprises the open reading frames ORF6 and ORF6/7 of E4.

34. (Amended) A defective recombinant adenovirus consisting essentially of

the ITR sequences,

an encapsulation sequence,

a heterologous DNA sequence, and

all or part of the E2 gene.

35. (Amended) A defective recombinant adenovirus consisting essentially of

the ITR sequences,

an encapsulation sequence,

a heterologous DNA sequence, and

all or part of the E4 gene.